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An investigation into the nature of non-voiding contractions resulting from detrusor hyperreflexia in neurogenic bladders following spinal cord injury

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14. ABSTRACT The purpose of this project is to determine the cause behind non-voiding contractions (NVC) of the bladder seen with filling following suprasacral spinal cord injury (SCI). The most significant findings over the course of the past year have been that NVC in chronic SCI are accompanied by intra-abdominal pressure increases resulting from abdominal wall contraction. The temporal relationship appears to be that of either the abdominal pressure rise beginning just prior to, or simultaneously with, the bladder pressure rise. These results, therefore, strongly suggesting that these abdominal wall-mediated abdominal pressure rises either cause NVC, or arise from the same mass reflex event as the NVC.					
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INTRODUCTION:

Suprasacral spinal cord injury (SCI) is often occasioned by numerous, rhythmic high pressure non-voiding contractions (NVC) during normal bladder filling. These NVC are responsible for incontinence episodes, bladder and bladder neck damage, as well as the life threatening consequences of hydronephrosis and autonomic dysreflexia. Our objectives and goals are to determine the relative contributions, if any, of the nervous system (parasympathetic, sympathetic and somatic) and intrinsic myogenic activity on the generation of high pressure NVC in chronic SCI rats with detrusor hyperreflexia and detrusor-sphincter dyssynergia. Once achieved, these insights may be translatable to novel therapeutic approaches toward alleviating detrusor hyperreflexia and detrusor-sphincter dyssynergia in humans with suprasacral spinal cord injury. Our overarching hypothesis is that NVCs in chronic SCI may be augmented by bladder-to-bladder parasympathetic reflexes, but are not themselves caused by bladder-to-bladder reflexes. Rather, two other sources are proposed: the first is myogenic filling contractions, which either invade the dome of the bladder causing a large amplitude myogenic contraction or cause a secondary reflex response to distension. This latter possibility is subtly yet importantly different than a response to gradual steady filling, as it implies an episodic distension of the dome which results in the spinal reflex. In either case, diminishing these myogenic contractions should reduce or eliminate the generation of large amplitude NVCs. The second possibility is one of indirect stimulation of the bladder by bladder-to-somatic reflexes, such that bladder filling, be it steady or episodic, evokes a limited mass-reflex of the abdominal musculature. This contraction of abdominal muscle then stimulates the bladder contraction by pressure generation via compression.

BODY: The approved tasks of the statement of work are as follows:

Task 1. Development, submission and approval of an IACUC protocol covering the intended research (2 months)

Task 1 was accomplished in Year 1 and we proceeded to Task 2.

Task 2. SA1: Determination of the autonomic neural and myogenic contribution to NVCs in conscious SCI rats. This task will take 18 rats/group in order to achieve 12 rats with detrusor hyperreflexia, detrusor-sphincter DSD and recovered voiding in order to achieve the aim's goals (75% of chronic SCI animals fall into this category, assume a loss of two animals/group due to morbidity/mortality associated with chronic SCI)

2a. Ordering of animals, initial surgical preparation of SCI rats (1.25 months)

2b. Weekly experiments with random assignments of animals to either treatments consistent with SA1a, SA1b, SA1c or Control across a 14.5 month period (15.5 months, includes 4 weeks of vacation/holiday time in addition to the 16.5 month experiment period)

2c. Final data analysis (data analysis will be ongoing throughout, this will represent the finalization of data period, 0.25 months)

Total Time for Task 2 – 17 months

Total Time for Tasks 1 and 2 – 19 months

Task 2 was nearly completely accomplished. We accomplished Sub-Tasks 2a and 2b. As of 9/2/14, we have completed much of the data analysis (Sub-Task 2c; see below for results). Analysis of abdominal contraction and bladder contraction correlation, and the effects of the various treatments on this relationship, is still underway.

Table 1: The following Treatments were delivered to awake, restrained chronic SCI rats during transvesical cystometric evaluation with simultaneous abdominal balloon catheter pressure measurements. For graphical representation of the results, 1st Treatment will be referred to as Vehicle, 2nd Treatment as Drug 1, 3rd Treatment as Drug 2, and 4th Treatment as Drug 4 (Figures 1 and 2). For the purposes of ANOVA, Groups were referred to as Class and Drug as Treatment. All data were normalized for each animal to its 1st Treatment Vehicle response. Results are described as Mean data, but illustrated graphically as Median with Ranges.

Group	1st Treatment	2nd Treatment	3rd Treatment	4th Treatment
SA1a – Parasympathetic antagonists	Vehicle	Atropine (0.4 mg/kg)	NF-449 (10 mg/kg)	Hexamethonium (25 mg/kg)
SA1b – Sympathetic antagonists	Vehicle	Phentolamine (10 mg/kg)	Propranolol + SR 59230A (1 mg/kg / 1 mg/kg)	Hexamethonium (25 mg/kg)
SA1c – Smooth muscle blockers	Vehicle	Nifedipine (30 mg/kg)	CL-316243 (100 µg/kg)	Isoproterenol (100 µg/kg)
Control	Vehicle	Vehicle	Vehicle	Vehicle

In some instances, drug treatments resulted in overflow incontinence, which precluded the collection of certain data points (Functional Bladder Capacity, Voiding Efficiency, and Maximal Bladder Contraction Amplitude). The first sign of leak during overflow was used to designate True Bladder Capacity under these conditions (reflects actual mechanical capacity has been attained). No significant effect of repeated vehicle administration was seen on any parameters.

For True Bladder Capacity (TBC; Figure 1), 2-Way RM ANOVA comparing all groups revealed highly significant results for Interaction, Class and Treatment ($P < 0.0001$ for all). For parasympathetic antagonists (SA1a), Atropine resulted in a significant increase (~60%, $P < 0.01$) in TBC that was maintained and/or enhanced by NF-449 (~77%, $P < 0.0001$). Addition of Hexamethonium resulted in an even greater enhancement (~130%, $P < 0.0001$). For sympathetic blockers (SA1b), only total autonomic blockade by hexamethonium resulted in a significant increase (~130%, similar to the effect seen in SA1a). For smooth muscle relaxants (SA1c), Verapamil had no effect, while CL-316,243 resulted in a ~30% increase ($P < 0.05$) and Isoproterenol resulted in an additional increase to ~130% of Vehicle control ($P < 0.05$). Figure 1 details the results of within group statistical analysis, that of the Drug Treatments vs. within group Vehicle Controls.

In contrast, for Functional Bladder Capacity (FBC; Figure 1), 2-Way RM ANOVA comparing all groups showed no statistically significant effects, although Treatment approached significance at $P=0.0777$. Post-hoc comparison to repeated vehicle alone revealed a significant enhancement of FBC (~170%) following NF-449. Figure 1 details the results of the analysis of within group comparisons to Vehicle Control, and here one can see an effect of Phentolamine (SA1b; ~155%, $P<0.001$) and Isoproterenol (SA1c; ~150%, $P<0.01$).

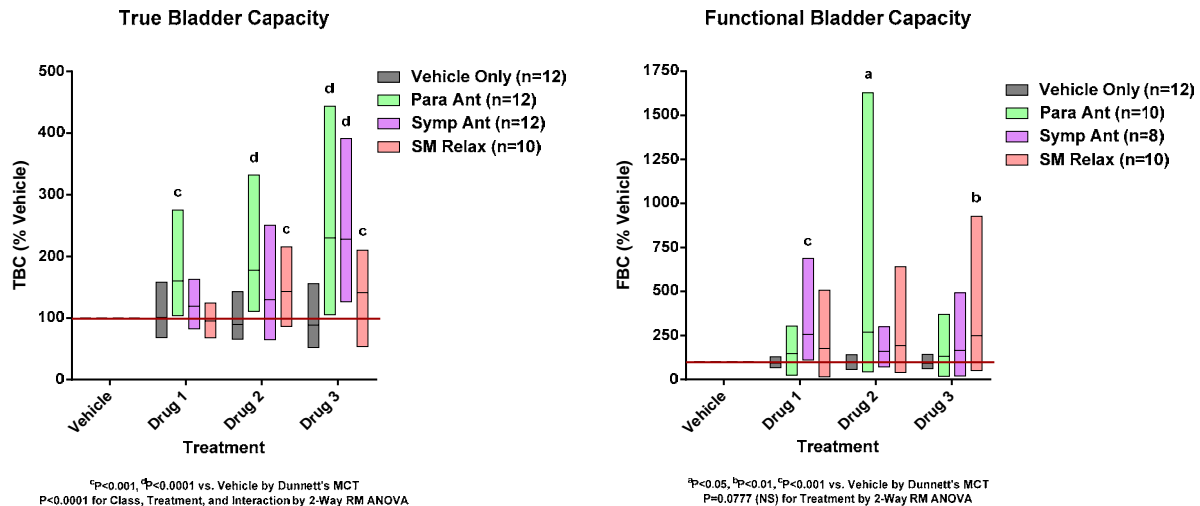


Figure 1 – Graphical representations of the medians and ranges of the effects of repeated vehicle or drug treatments on True and Functional Bladder Capacity. Data from each animal were normalized to their Vehicle Control. Letter designations above bars indicate statistical significance vs. within group Vehicle controls using Dunnett's multiple comparison test following 2-Way RM ANOVA (a,b,c and d represent $P<0.05$, 0.01 , 0.001 and 0.0001 , respectively). Drug 1 – 3 refer to the treatments indicated in Table 1. Note no significant effect of repeated vehicle on these parameters of neurogenic bladder function.

For Voiding Efficiency (VE; Figure 2), 2-Way RM ANOVA comparing all groups revealed no significant effects. Figure 2 shows the results of within group comparisons to Vehicle Control. As seen with FBC, phentolamine (SA1b) resulted in an enhanced voiding efficiency (~130%, $P<0.01$) and for Smooth Muscle Relaxants (SA1c), Verapamil and Isoproterenol both significantly enhanced voiding efficiency (~75% and $P<0.05$ for both). Note that the patterns for FBC and VE are similar, as these are related factors.

For Maximal Bladder Contraction Amplitude during Voiding (Max BCA; Figure 2), 2-Way RM ANOVA comparing all groups revealed significant effects for Class ($P=0.0055$), Treatment ($P=0.0077$) and Interaction ($P=0.0061$). When compared to repeated vehicle controls, Atropine (SA1a) resulted in a significant decrease in Max BCA (~23%, $P<0.01$), and NF-449 maintained this decrease (~17%, $P<0.05$). No treatments from sympathetic blockade (SA1b) affected Max BCA. Smooth muscle relaxants (SA1c), CL-316 and Isoproterenol, both resulted in ~16% decrease ($P<0.05$ for both).

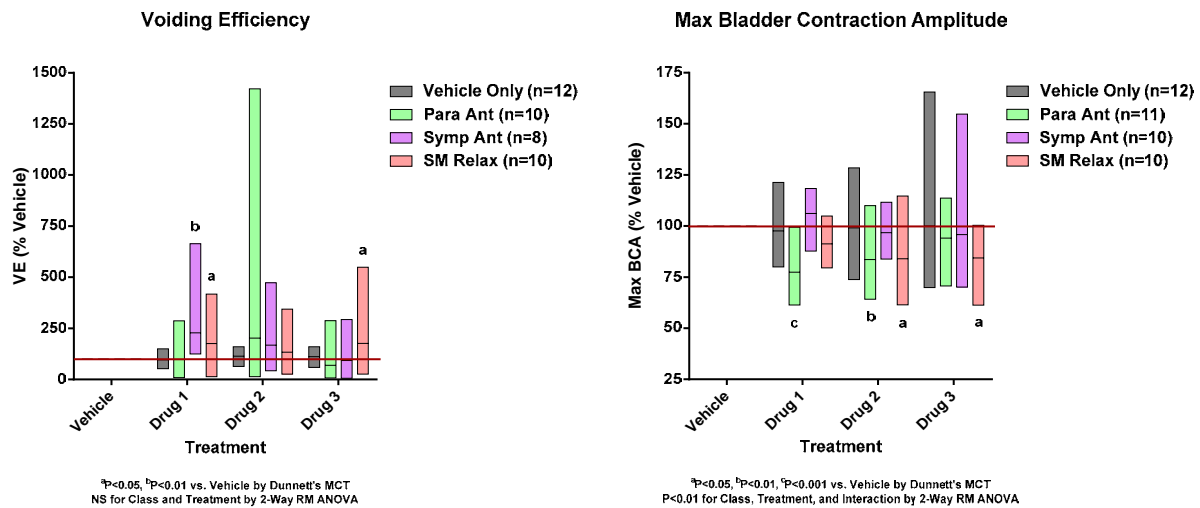


Figure 2 – Graphical representations of the medians and ranges of the effects of repeated vehicle or drug treatments on VE and Max BCA. Data from each animal were normalized to their Vehicle Control. Letter designations above bars indicate statistical significance vs. within group Vehicle controls using Dunnett's multiple comparison test following 2-Way RM ANOVA (a,b,c and d represent P<0.05, 0.01, 0.001 and 0.0001, respectively). Drug 1 – 3 refer to the treatments indicated in Table 1. Note no significant effect of repeated vehicle on these parameters of neurogenic bladder function.

For non-voiding contractions (NVC) during filling, we were unable to detect any specific effect of any drug treatment on total NVC Count (although both Vehicle Alone and Para Ant appeared elevated with post-vehicle control treatment; P=0.0029 and P=0.0099 for Treatment when comparing all groups and when comparing repeated vehicle controls to parasympathetic antagonists, respectively, by 2-Way RM ANOVA; Figure 3).

For maximal NVC amplitude (Max NVC Amp; Figure 3), comparison of parasympathetic antagonists to repeated vehicle alone by 2-Way RM ANOVA revealed P=0.0004 for Interaction, P=0.0090 for Treatment and P=0.0422 for Class, with NF-44 resulting in significantly lower Max NVC Amp than matched vehicle alone (76%, P<0.0001).

For Area Under the Curve of Filling Pressure, a combined measure of Compliance and NVC considered important in diagnosis of "High Pressure Bladders" in patients, comparison across Classes revealed significant effects (P=0.0002 for Interaction, P=0.0001 for Treatment and P=0.0142 for Class). Post-hoc analysis shows that Hexamethonium was the dominant treatment, resulting in an increase to 272% and 297% Fill AUC for Para Ant and Symp Ant, respectively (P<0.0001 vs. sequenced-matched Vehicle Alone, and P<0.05 and P<0.01 vs. Isoproterenol, respectively).

Direct measurement of Compliance across Classes revealed a significant Treatment effect (P=0.0225), with a 3-fold increase in compliance due to the beta3-adrenergic agonist, CL-316,243 of the Smooth Muscle Relaxants (P<0.05 vs. sequence matched Para Ant and Symp Ant, and P<0.01 for Repeated Vehicle).

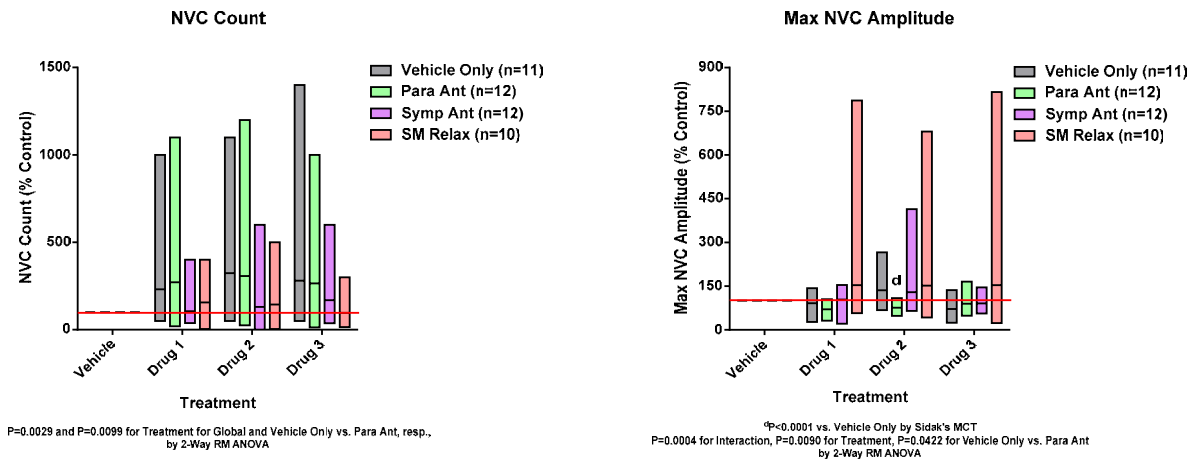


Figure 3 – Graphical representations of the medians and ranges of the effects of repeated vehicle or drug treatments on NVC Count and Max NVC Amp. Data from each animal were normalized to their Vehicle Control. Letter designations above bars indicate statistical significance vs. within group Vehicle controls using Dunnett's multiple comparison test following 2-Way RM ANOVA (a,b,c and d represent P<0.05, 0.01, 0.001 and 0.0001, respectively). Drug 1 – 3 refer to the treatments indicated in Table 1. Note no significant effect of repeated vehicle on these parameters of neurogenic bladder function.

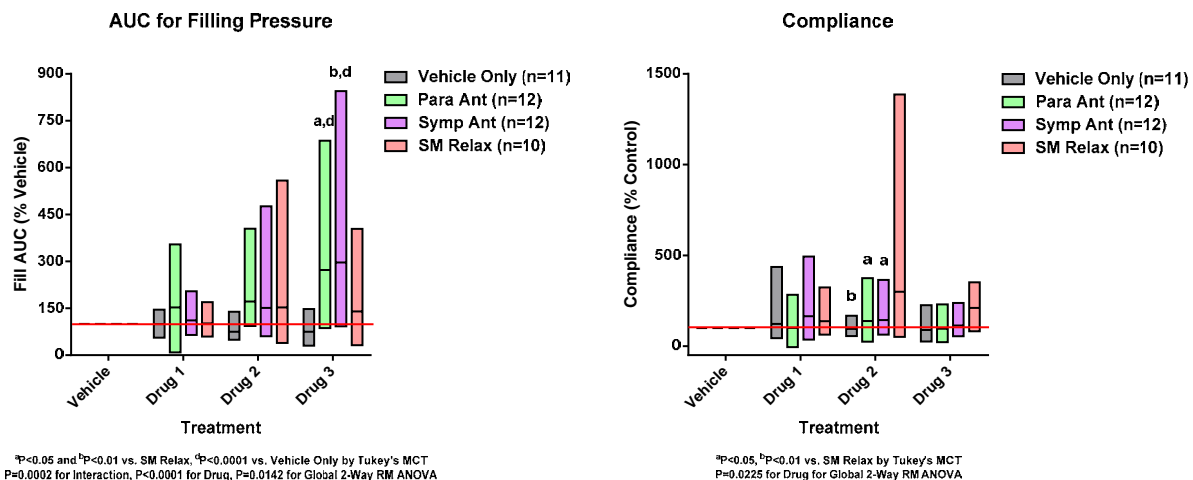


Figure 4 – Graphical representations of the medians and ranges of the effects of repeated vehicle or drug treatments on AUC for Filling Pressure and filling Compliance. Data from each animal were normalized to their Vehicle Control. Letter designations above bars indicate statistical significance vs. within group Vehicle controls using Dunnett's multiple comparison test following 2-Way RM ANOVA (a,b,c and d represent P<0.05, 0.01, 0.001 and 0.0001, respectively). Drug 1 – 3 refer to the treatments indicated in Table 1. Note no significant effect of repeated vehicle on these parameters of neurogenic bladder function.

The results from parasympathetic blockade (SA1a) and smooth muscle direct relaxation (SA1c) are not surprising in terms of TBC. The results from the sympathetic blockade was somewhat surprising; that direct sympathetic blockade at alpha-adrenergic receptors did not also

increase TBC was somewhat surprising, given the use of this strategy to treat SCI patients. Additionally, that blockade of beta-adrenergic receptors did not result in a reduction of TBC suggests that ongoing sympathetic inhibition is not occurring in chronic SCI rats, and this may be supported by positive the response to beta-receptor agonists.

That FBC and VE were positively affected by phentolamine (SA1b) is not inconsistent with previous is consistent with smooth muscle dyssynergia during voiding in chronic SCI. This is additionally supported by the positive effects of smooth muscle relaxants (SA1c) acting at the level of the urethral smooth muscle. Surprising was the result that NF-449 (SA1a) should enhance FBC (and VE, albeit not significantly). This may suggest a role for purinergics in the urethra, at least in in chronic SCI.

That Max BCA during voiding is reduced by parasympathetic antagonists (SA1a) and beta-adrenergic antagonists (SA1c) is not surprising, although the reason for their effects is mechanistically different (the former acts to weaken the voiding contraction while the latter act to relax the outlet; as it becomes an open system, both bladder force and urethral resistance play a role in Max BCA during voiding).

The results on NVC parameters (Count and Max Amp) were somewhat surprising, given historical data of dose-responses for the compounds involved. For example, we expected that atropine should result in an increased Count and decreased Max Amp, and CL-316,243 should have resulted in a decrease in count and likely a decrease in Max Amp. In this case, it may be that the repeated vehicle alone results largely obfuscate any Drug effects. We intend to reanalyze the data using non-parametric 2-Way ANOVA to better address possible drug effects.

That Hexamethonium resulted in an increased Fill AUC is largely due to the effect of increased TBC and areflexia resulting in overflow incontinence at high pressures. This result should not be considered physiologically relevant.

The positive effect of the beta3-adrenergic agonist on Filling Compliance is not unexpected, and is in keeping with the mechanism of action for this compound.

Task 3. SA2: Determination of extra-vesicular contributions to NVCs in decerebrate chronic SCI rats. A total of 20 rats will be required to achieve this aim's goal. 18 for the same reasons as given for each group size in Task 2, and an additional 2 rats for mortality/morbidity due to decerebration.

3a. Ordering of animals, initial surgical preparation of SCI rats (1.25 months, but happened during Task 2, so not counted within Task 3)

3b. Weekly experiments across a 4.5 month period.

3c. Data analysis and report writing – ongoing and finalized within 0.5 months.

Total Time for Task 3 – 5 months

Total Time for Entire Project – 24 months

We have initiated SA2, and had a rather steep learning curve regarding decerebration and tracheal tube implant in general (both of which were fine alone, but combined were problematic)

for chronic SCI rats, and then secondarily for achieving the open abdomen. I had initially believed that twisting the animal with abdomen up while its head was still mounted in the stereotaxic would work, as this is how we had done similar experiments when I was back in Pittsburgh. However, we had difficulties with this in combination with the tracheal tube for respiration and for opening the abdomen to relieve abdominal pressure. A further unexpected complication was a dramatic increase in lower abdominal somatic activity, for which we have no explanation at the present (all animals are verified to be completely transected at T9-10, therefore it is counterintuitive to imagine that decerebration would affect somatic activity distal to the SCI – there may be something humoral or vagal involved in this response).

We have since remedied these issues and have deconstructed and reconstructed a stereotaxic head stage in order to completely flip the animal. The trachea tube issue was remedied by straightening the P240 tubing and maintaining a flat position with regard to the ear bars under these conditions. Preliminary results are available from 3 animals thus far, and while the results suggest a strong interaction with abdominal pressure and bladder pressure, it seems that the bladder is driving the abdomen at this point (Figures 5 and 6). Previously reported (Q1 Annual Report) abdominal pressure increases leading bladder contractions may still suggest a two way interaction. While one can easily imagine abdominal pressure impacting bladder pressure directly, the reverse must be through reflex pathways.

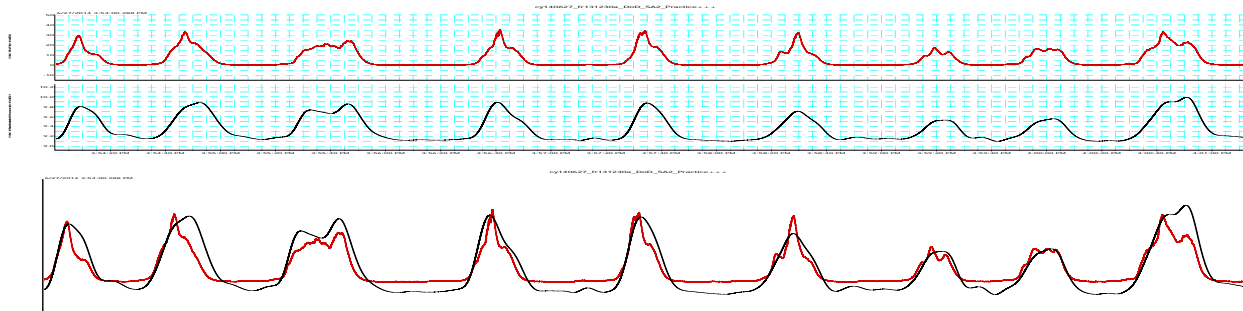


Figure 5 – Top Panels (green grid backgrounds) show bladder pressure waves (top most, red) and abdominal pressure waves (bottom-most, black) during cystometry with a closed abdomen in a decerebrate chronic SCI animal. The bottom panel shows the traces superimposed. Note the rather high fidelity between the two pressures, strongly suggesting an intimate relationship between the two sources.

When the abdomens of the animals are opened, one sees an almost complete abolition of the abdominal pressure waves, while maintaining the bladder pressure waves, albeit at a lower amplitude. These data suggest that the bladder is driving the abdomen and that the resultant higher pressures are due to both sets of muscle contracting. Continued studies will include neuromuscular blockade.

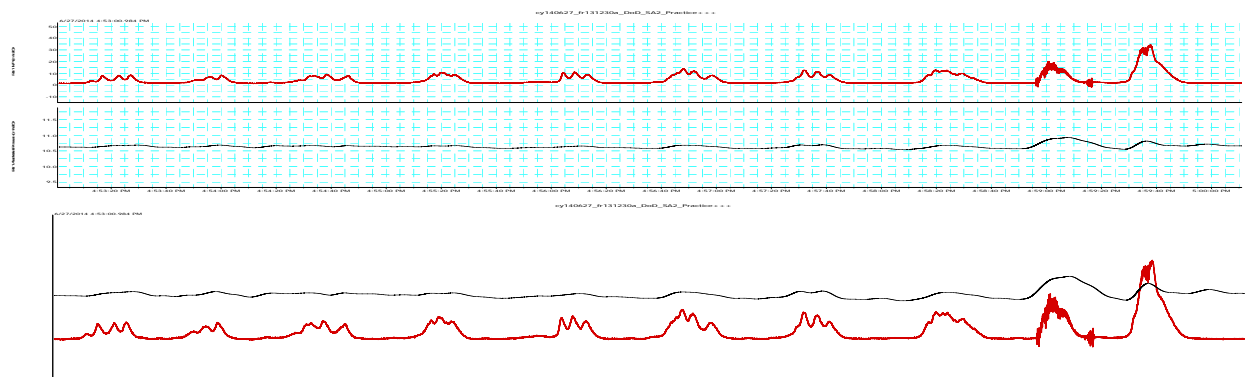


Figure 6 – Top Panels (green grip backgrounds) show bladder pressure waves (top most, red) and abdominal pressure waves (bottom-most, black). The bottom panel shows the traces superimposed.

KEY RESEARCH ACCOMPLISHMENTS:

- Analysis of standard cystometric results from 46 successful experiments from SA1.
- Trouble shooting issues concerning combinations of SCI, decerebration, tracheal intubation and abdominal opening for video recording. This included construction of a novel stereotaxic setup.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- The results of SA1 have been submitted to the Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU; Abstract Appended), and are being prepared for manuscript write up.

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

We have thus far demonstrated that repeated vehicle administration does not significantly affect TBC, FBC, VE, Max BCA, NVC Count or Max NVC Amplitude, AUC for Filling Pressure or Filling Compliance. We have observed expected outcomes for many of the drugs given, with the exception of NVC parameters. We will reanalyze all data by non-parametric 2-Way RM ANOVA in order to eliminate any non-Gaussian variances that may obfuscate results, given the relatively low N/group for the number of groups being compared (i.e. the variance in results seen with the Vehicle Alone groups may be problematic for these analyses).

We have also observed that intra-abdominal pressure and intravesical pressure have an intimate relationship, suggesting one drives the other, and that may be different depending on the event (baseline vs. NVC). Together with Specific Aim 2, we are poised to determine the relationship between the bladder-to-bladder reflex and either a bladder-to-abdominal musculature-bladder reflex or a bladder-to-mass reflex which drives them both simultaneously.

These results are important, as they will elucidate the relationship(s) between the urinary bladder and the somatic motor system following suprasacral SCI, and provide further evidence for or against certain treatment approaches that are or could be utilized to treat neurogenic hyperreflexic bladders in suprasacral lesion SCI patients.

PROBLEMS/ISSUES/FUTURE PLANS:

We plan to reanalyze the data using non-parametric statistics in order to reduce the effect of non-Gaussian variability on our analyses. We will analyze the Abdominal Contraction data from SA1, and we will continue collecting data for SA2.

REFERENCES:

None

APPENDICES:

Submitted Abstract to the Annual SUFU Winter Meeting:

DIFFERENTIAL EFFECTS OF STEPWISE PHARMACOLOGICAL AUTONOMIC DENERVATION OR DIRECT SMOOTH MUSCLE RELAXATION ON URODYNAMIC INDICES IN CHRONIC SPINAL CORD INJURED RATS

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Introduction: Suprasacral spinal cord injury (SCI) often results in detrusor overactivity, causing low compliance (Comp) and unsafe bladder pressures. We determined the relative contributions of parasympathetic and sympathetic nervous systems and spontaneous myogenic activity on urodynamic indices in chronic SCI rats.

Methods: Chronic female SCI rats (>4 weeks) underwent conscious cystometry and i.v. drug treatment to achieve parasympathetic (Para) or sympathetic (Symp) denervation or direct smooth muscle relaxation (SM; n=10-12/ group). Following control cystometry, vehicle was administered in all rats. Control group animals received 3 additional vehicle doses. In the Para group, rats sequentially received atropine (antimuscarinic), NF-449 (purinergic antagonist) and hexamethonium (HEX, autonomic ganglion blocker). The Symp rats received phentolamine (P; α -adrenergic antagonist), propranolol + SR59230A (complete β -adrenergic block) and HEX. The SM rats received verapamil (Ca²⁺ channel blocker), CL-316,243 (β 3-adrenergic agonist) and isoproterenol (β 1-3-adrenergic agonist). Data were analyzed by 2-Way RM ANOVA, alpha = 0.05.

Results: As can be seen in the table, selective Para resulted in increased true bladder capacity (TBC) and area under the curve for filling pressure (AUC-FP), and decreased maximal bladder contraction amplitudes for voiding (BCA-V) and nonvoiding events. Selective Symp had no effect except the P increased functional bladder capacity (FBC) and voiding efficiency. HEX increased TBC and AUC-FP in both autonomic arms. SM increased TBC, FBC, and Comp and decreased BCA-V.

		Treatment					Treatment		
		Drug 1	Drug 2	Drug 3			Drug 1	Drug 2	Drug 3
True Bladder Capacity					Compliance				
	Para	60%↑*	77%↑****	130%↑****		Para	—	—	—
	Symp	—	—	128%↑****		Symp	—	—	—
	SM	—	42%↑*	41%↑**		SM	—	200%↑*	—
Functional Bladder Capacity					AUC of Filling Pressure				
	Para	—	—	—		Para	—	71%↑*	172%↑****
	Symp	155%↑***	—	—		Symp	—	—	197%↑****
	SM	—	—	149%↑*		SM	—	53%↑*	—
Voiding Efficiency					NVC Count				
	Para	—	—	—		Para	—	—	—
	Symp	128%↑**	—	—		Symp	—	—	—
	SM	—	—	—		SM	—	—	—
Max Bladder Contraction Amplitude (voiding)					Max Bladder Contraction Amplitude (nonvoiding)				
	Para	23%↓**	16%↓*	—		Para	—	24%↓****	—
	Symp	—	—	—		Symp	—	—	—
	SM	—	—	16%↓*		SM	—	—	—

Conclusions: That specific Para increased TBC and Symp had no effect suggests ongoing Para tone during filling with no such influence of Symp. Only α -adrenergic blockade had any effect in Symp, and that was likely on urethral smooth muscle dyssynergia. A strategy combining antimuscarinic, α -adrenergic blockade and direct bladder smooth muscle relaxation may ultimately provide the best therapeutic results.

Funding Source: DoD, SCIRP IIR—SC110031 to MOF